Dynamic Kinetic Resolutions

A MacMillan Group Meeting
Presented by Jake Wiener
On the sixth day of June, two thousand and two, at eight o'clock in the evening.

I. Overview of concept. Contrast to other types of resolutions.
II. Chemical methods.
III. Combined chemical/biocatalytic methods.

Relevant reviews:
Stecher, H.; Faber, K. *Syntheses*, 1997, 1. (Biacatalytic dynamic kinetic resolutions only)

Dynamic Kinetic Resolution vs. Other Types of Resolutions

- **Kinetic Resolution:** One enantiomer reacts much faster than the other

\[
\text{Me} \quad \text{Ti(O-Pr)}_4 \quad \text{(L)} \rightarrow \text{Me}
\]

\[
\begin{array}{c}
\text{CH} \\
\text{Me}
\end{array} \quad \text{Me} \quad \text{Me}
\]

\[
> 96\% \text{ ee}
\]

\[
55\% \text{ conversion} \\
98:2 \text{ dr} \\
> 96\% \text{ ee}
\]

- **Parallel Kinetic Resolution:** Each enantiomer undergoes a different reaction

\[
\begin{array}{c}
\text{Me} \\
\text{CF}_3\text{CH}_2\text{OH}
\end{array} \quad \text{(DHQD)}_2\text{AQN}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{OCH}_2\text{CF}_3
\end{array} \quad \text{Me} \\
\text{OCH}_2\text{CF}_3
\]

\[
93\% \text{ ee} \\
36\% \text{ yield}
\]

\[
80\% \text{ ee} \\
41\% \text{ yield}
\]


- In dynamic kinetic resolutions, 100% of racemic SM can be converted to enantiopure product
Dynamic Kinetic Resolution: Overview

- Kinetic Resolution
  \[ \text{OH} \rightarrow_k \text{X} \]

- Dynamic Kinetic Resolution
  \[ \text{OH} \rightarrow_k \text{X} \]

50% theoretical yield of A

- In a DKR, as with a classical KR, one enantiomer reacts slowly under the reaction conditions
- In a DKR, the rate of racemization of SM is fast relative to the rate of the asymmetric transformation
- Thus, using DKR, possible to convert 100% of racemic SM to enantiopure product due to equilibrating racemization of SM
- How can we control the two processes: racemization and asymmetric transformation?

First Reported Chemical Dynamic Kinetic Resolution: \( \beta \)-Keto Ester Reduction

- Tai observes DKR phenomenon in 1979

\[
\begin{align*}
\text{MeO} \quad \text{Et} & \quad \text{MeO} \quad \text{Et} \\
\text{MeO} \quad \text{Et} & \quad \text{MeO} \quad \text{Et}
\end{align*}
\]

\[
\text{cat. (R,R)-Tartaric Acid—MN} \quad \text{H}_2 \quad \text{MeO} \quad \text{Et} \quad \text{MeO} \quad \text{Et}
\]

(2S, 3R)

- (2S) isomer attributed to influence of catalyst on epimerization of SM after complexation but prior to reduction

Chemical Dynamic Kinetic Resolution: Noyori Reductions

Noyori β-keto ester reductions describe relative rates

\[
\begin{align*}
0.4 \text{ mol\% (R)-BINAP-Ru(II)} & \rightarrow 0.4 \text{ mol\% (R)-BINAP-Ru(II)} \\
\text{H}_2, \text{CH}_2\text{Cl}_2 & \\
94\% \text{ de (93\% ee)} & \\
k_{\text{fast}}/k_{\text{slow}} = 15 \\
k_{\text{inv}}/k_{\text{fast}} = 6.1 \\
k_{\text{inv}}/k_{\text{slow}} = 92
\end{align*}
\]


"The absolute configuration at C-3 is governed by the handedness of the BINAP ligand while the C-2 configuration is dependent on substrate structures."

Noyori, JACS, 1989, 111, 9135.

Chemical Dynamic Kinetic Resolution: Noyori Reductions
computations predict relative rates of reactions of enantiomers

Chiral Ru(II) complex catalyzes benzil reduction

\[
\begin{align*}
\text{Ph}_2\text{C} & \rightarrow \text{Ph}_2\text{CH} \\
\text{Ph}_2\text{C} & \rightarrow \text{Ph}_2\text{CH} \\
\text{Ph}_2\text{C} & \rightarrow \text{Ph}_2\text{CH} \\
\text{Ph}_2\text{C} & \rightarrow \text{Ph}_2\text{CH} \\
100\% \text{ yield} & \\
>99\% \text{ ee} & \\
\text{chiral: meso} = 9:1 &
\end{align*}
\]

Chemical Dynamic Kinetic Resolution: Ru(II) Reductions in Synthesis

- Formal synthesis of (−)-Balanol 1 proceeds through (2S,3R)-3-hydroxysilane 2.

![Chemical structure of 1 and 2](image)

- Ru(II) catalyzed DKR provides key step in synthesis of 2.

![Chemical reaction](image)


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Chemical Dynamic Kinetic Resolution: Conjugate Reduction

racemization of starting material induced by added base

1. 10 mol% CuCl(S)-p-tol-BINAP
   NaOt-Bu (1.7 eq)
   t-BuOH (5.0 eq)
   PMHS (2.2 eq)
   toluene, 26 h
2. TBAF

A variety of alkyl, aryl substituents at positions 3 and 5 are tolerated

- Product trapped as enol silane to prevent epimerization

![Chemical mechanism](image)

Without base, a classical KR is observed; choice of base is crucial for DKR.

Chemical Dynamic Kinetic Resolution: Epoxide Opening

- LiBr is required for racemization and subsequent DKR
  
  ![Chemical structure of epoxide opening reaction](image)

- Exceptionally high ee attributed to further resolution of minor product
  
  ![Chemical structure of epoxide opening reaction](image)

  Jacobsen, JACS, 1999, 121, 6086.

Chemical Dynamic Kinetic Resolution: Azlactone and Dioxolanedione Opening

- Azlactones (pKa ~ 9) have good propensity for racemization; DMAP known to catalyze alcohols

  ![Chemical structure of azlactone opening reaction](image)

  Fu, JOC, 1998, 63, 3154.

- Modifies Cinchona alkaloid: Bifunctional organic catalyst

  ![Chemical structure of dioxolanedione opening reaction](image)

  Deng, JACS, 2002, 124, 2870.

Chemical Dynamic Kinetic Resolution: \( \pi \)-allyl Pd Catalysis

- Equilibration between diastereomers is not a trivial problem

\[
\text{enantiomers} \quad \begin{array}{c}
\text{OH} \\
R_1 R_2 \\
\leftrightarrow \quad \text{OH} \\
R_1 R_2
\end{array} \quad \begin{array}{c}
k_{\text{rac}} \\
- k_{\text{rac}}
\end{array} \quad \begin{array}{c}
k_{\text{eq}} = - k_{\text{rac}}
\end{array} \quad \begin{array}{c}
k_{\text{inv}} \\
- k_{\text{inv}}
\end{array} \quad \text{diastereomers}
\]

The rates of epimerization of two diastereomers are not necessarily equal

- Enhanced diastereomeric ratio after internal trapping suggests rapid equilibration of Pd complexes

\[
\begin{aligned}
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{Bn} \\
\text{N} & \quad \text{O}
\end{aligned} \quad \xrightarrow{\text{Pd}} \\
\begin{aligned}
\text{Ph} & \quad \text{Bn} \\
\text{N} & \quad \text{O}
\end{aligned}
\]

Product oxazolines are also ionized by the catalyst, giving rise to thermodynamic product mixtures

Can the epimerizing intermediates be irreversibly trapped with nitrogen nucleophiles in a DKR?

Chemical Dynamic Kinetic Resolution: \( \pi \)-allyl Pd Catalysis

- Phthalamide is able to trap intermediates in a dynamic kinetic resolution

\[
\begin{aligned}
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{Me}
\end{aligned} \quad \xrightarrow{1 \text{ mol\% Pd}^0 - \text{dppe}} \\
\text{phthalamide} \quad \begin{array}{c}
\text{OH} \\
\text{Me}
\end{array} \quad \xrightarrow{20 \text{ h}, \text{RT}, \text{THF}} \quad \begin{array}{c}
\text{NHCOPh} \\
\text{Me}
\end{array}
\]

As size of substituent increases, so does diastereoselectivity

- Chiral ligands on Pd afford matched/mismatched cases

\[
\begin{aligned}
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{Me}
\end{aligned} \quad \xrightarrow{1 \text{ mol\% Pd}^0} \\
\text{(S) - BINAP} \quad \begin{array}{c}
\text{NHCOPh} \\
\text{Me}
\end{array}
\]

\[
\begin{aligned}
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{Me}
\end{aligned} \quad \xrightarrow{\text{Pd}^0} \\
\text{(R) - BINAP} \quad \begin{array}{c}
\text{NHCOPh} \\
\text{Me}
\end{array}
\]

Chemical Dynamic Kinetic Resolution: \(\pi\)-allyl Pd Catalysis

- Chiral catalyst effectively opens diene monoepoxides - Trost

\[
\text{CH}_2=CH-CH=CH-OH \quad \xrightarrow{2.5\% \text{Pd}^0\text{Ln}^+} \quad \text{CH}_2=CH-CH=CH-\text{OH} + 5\% \text{Na}_2\text{CO}_3
\]

- Epoxide opening facilitates synthesis of anti-epileptic drug Vigabatrin

\[
\text{CH}_2=CH-CH=CH-OH \quad \xrightarrow{\text{Tl}_2\text{O}} \quad \text{CH}_2=CH-CH=CH-OH + 97\% \text{yield}
\]

\[
\text{CH}_2=CH-CH=CH-OH \quad \xrightarrow{\text{THF}, 0 °C} \quad \text{CH}_2=CH-CH=CH-\text{CH}_2\text{CO}_2\text{CH}_3 + 64\% \text{yield}
\]

\[
\text{OH} \quad \xrightarrow{\text{i. 6N HCl}} \quad \text{Cl} \quad \xrightarrow{\text{ii. Ion exchange resin}} \quad \text{NH}_3
\]

\[
(\text{R}) - \text{Vigabatrin}
\]


Chemical Dynamic Kinetic Resolution: Silylated \(\alpha\)-Amino Acid Synthesis

- Racemic zirconiaaziridines are readily available

\[
\text{Cp}_2\text{ZrCl}_2 \quad \xrightarrow{1. \text{eq. BuLi}} \quad \text{Cp}_2\text{Zr}N\text{Ph} \quad \xrightarrow{2. \text{THF, } -78 °C \text{ to RT, 6h, 60%}} \quad \text{Cp}_2\text{Zr}N\text{Ph}
\]

- DKR of zirconiaaziridines affords unnatural \(\alpha\)-amino acids

\[
\text{Cp}_2\text{Zr}N\text{Ph} \quad \xrightarrow{2-3 \text{hour syringe pump addition}} \quad \text{Cp}_2\text{Zr}N\text{Ph}
\]

Syringe pump addition required to achieve high selectivity due to slow racemization of SM relative to insertion

Norton, *JOC*, ASAP

**Chemical Dynamic Kinetic Resolution: Displacements via Chiral Auxiliaries**

- Chiral sultam facilitates highly selective $S_N2$ DKR

![Chemical structure](image)

SM epimerizes under reaction conditions; one diastereomer much more reactive than the other.

**Biocatalytic Dynamic Kinetic Resolution: Enzymatic Reduction**

- Relatively simple substrates are reduced in biocatalytic DKR

![Biocatalytic structure](image)

Recombinant *E. coli* expressing Gre3p

81% yield

> 98% ee

> 98% de

Recombinant *E. coli* express enzymes from Baker's yeast which catalyze DKR.

87% yield

> 98% ee

> 98% de

Biocatalytic Dynamic Kinetic Resolution: Pd\(^0\) in Allylic Acetate Hydrolysis

- Organometallic and biological reagents can be used in tandem?

\[
\text{R}^\alpha-\text{Pd} \xrightarrow{\text{enzyme}} \text{R}^\alpha-\text{OH}
\]

A selective enzyme is crucial
Organometallic catalyst must racemize substrate
Catalyst must not influence selectivity/reactivity of enzyme

- \(\pi\)-allyl Pd complex results in facile epimerization

\[
\begin{align*}
\text{Ph} & \quad \text{5 mol\% [PdCl}_2-(\text{MeCN})_2] \\
\text{Ph} & \quad 0.1 \text{ M phosphate buffer} \\
\text{COAc} & \quad \text{lipase from Pseudomonas fluorescens} \\
\end{align*}
\]

81\% yield
96\% ee
19 days

Biocatalytic Dynamic Kinetic Resolution: Esterification via Ru-Catalyzed Racemization

- How else can organometallic and biological reagents be used in tandem?

- Backvall Ru catalyst can function without interfering with enzymes

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{CO}_{3}\text{Me} & \quad \text{Ru catalyst} \\
\text{OH} & \quad \text{Ph} \\
\text{CO}_{3}\text{Me} & \quad \text{cyclohexane, 60 °C} \\
\text{racemic} & \quad \text{racemic}
\end{align*}
\]

Requirements for metal catalyzed racemization: No Base
1. No interference with enzyme in esterification
2. No direct base-catalyzed esterification

- Ru complex functions by dissociative mechanism

For a related process see: Park, JOC, 2001, 66, 4736.
Biocatalytic Dynamic Kinetic Resolution: Esterification via Ru-Catalyzed Racemization
organometallic catalyst functions in tandem with enzyme

- Ru catalyzed racemization plus enzymatic esterification: DKR

\[
\text{PhCH(OH)CO}_2\text{Me} \xrightarrow{2 \text{ mol\% Ru catalyst}} \text{PhCH(OAc)}_2\text{Me}
\]
\[
\text{P. cepacia lipase}
\]
\[
4\text{-Cl-C}_6\text{H}_4\text{OAc}
\]
cyclohexane, 60 °C

80% yield
98% ee

- Variation: One-pot aldol reaction — DKR. First DKR of β-hydroxy esters.

\[
\text{PhCHO} \xrightarrow{i. \text{ LDA, THF}} \text{MeCO}_2\text{Et} \xrightarrow{\text{ii. NH}_2\text{Cl}} \text{PhCH(OAc)}_2\text{Et}
\]
\[
\text{6 \text{ mol\% Ru catalyst}}
\]
\[
\text{P. cepacia lipase}
\]
\[
4\text{-Cl-C}_6\text{H}_4\text{OAc}
\]
TBME, 60 °C, 6d

73% yield
95% ee

Substrate must have two differently sized groups adjacent to stereocenter
These two groups cannot exceed the size of the active site in the enzyme


Biocatalytic Dynamic Kinetic Resolution: Ester Hydrolysis

- α-bromo esters racemized by Br⁻, resolved by enzymatic hydrolysis

\[
\text{PhCH}(_2\text{Br})\text{OCH}_3 \xrightarrow{\text{CH}_3\text{P}^+\text{Ph}_3\text{Br}^-} \text{H}_2\text{O-MeOH}} \text{Br}^-\text{CH(OH)CO}_2\text{Ph}
\]

78% yield
79% ee

- Enantienriched carboxylate product cannot racemize

Biocatalytic Dynamic Kinetic Resolution: Unique Racemization Protocols

- Racemization via Schiff base intermediate/enzymatic aminolysis

\[
\begin{align*}
\text{PhNH}_2\text{OMe} & \quad \text{NH}_3 \\
\text{HO} & \quad \text{NH}_3 \\
\text{catalytic} & \quad \text{Candida antarctica lipase} \\
& \quad \text{tBuOH, } -20^\circ\text{C} \\
\text{readily epimerized} & \\
\end{align*}
\]

85% yield
88% ee

- Racemic and readily epimerizing hemithioacetal generated and resolved by enzyme

\[
\begin{align*}
\text{MeO} & \quad \text{SH} \\
\text{TESO} & \quad \text{TESO} \\
\text{OAc} & \quad \text{Pseudomonas fluorescens lipase} \\
\text{TBME, SiO}_2, \text{RT} & \\
\text{MeO} & \quad \text{MeO} \\
\text{SH} & \quad \text{OTES} \\
\text{OAc} & \quad \text{OTES} \\
\end{align*}
\]

87% yield
90% ee

\text{SiO}_2 \text{ promotes hemithioacetal epimerization via dissociation/recombination mechanism}

\text{In Conclusion}

\[
\begin{align*}
\text{OH} & \quad k_F \\
R_2 & \quad \text{fast} \\
R_1 & \quad \text{A} \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad k_f \\
R_2 & \quad \text{B} \\
R_1 & \\
\end{align*}
\]

If \( k_r > k_f \gg k_s \) 100% theoretical yield of A

Dynamic kinetic resolutions have attracted increased attention in the last decade as the need for inexpensive chiral materials has increased and as the understanding of asymmetric catalytic processes has blossomed.

Crucial to a successful DKR is simultaneous epimerization and resolution: What are ways to epimerize
i. in the presence of asymmetric catalysts (enzymes, metals)?
ii. without epimerizing enantio- and diastereo- enriched products?